

REMARKS

The pending Office Action addresses claims 1-6, all of which stand rejected. Applicants respectfully request reconsideration based on the remarks submitted herewith.

At the outset, Applicants thank the Examiner for extending the courtesy of a telephone interview on February 23, 2009, with the undersigned attorney, attorney George A. Xixis, and Applicant Alastair Hodges for Applicants. During the interview, U.S. Patent No. 5,437,999 of Diebold et al., U.S. Patent No. 5,243,516 of White, the cited article written by Denuault et al., and the cited article written by Daruházi et al. were discussed. Although no agreement was reached, Applicants believe that the discussions about the references assisted all of the participating parties in better understanding each party's interpretation of the references.

Claim Amendments

Applicants amend claim 1 to clarify that the electrodes not being co-planar meant that the working electrode and the counter electrode or counter/reference electrode are located on different planes. Support for this amendment can be found throughout the specification, for example at paragraph [0066] and FIG. 12 of the published application. Applicants also amend claim 1 to clarify that the means for measuring from cell current the diffusion coefficient of a redox mediator in the cell and independently its concentration is circuitry configured to determine the diffusion coefficient of a redox mediator in the cell, and independently its concentration, from cell current. Support for this amendment can be found throughout the specification, for example at paragraph [0076] of the published application. Neither of these amendments affect the substance of the claims, and neither is made to overcome any prior art rejections. Rather, both amendments are made for the sake of providing clarity.

Applicants also add new dependent claims 7-11. Claim 7 recites that the circuitry includes a microprocessor. Support for this amendment can be found throughout the specification, for example at paragraph [0076] of the published application. Claim 8 recites that the working and the counter electrode or counter/reference electrode are planar electrodes. Support for this amendment can be found throughout the specification, for example at paragraph [0084] of the published application. Claim 9 recites that the circuitry is configured to achieve a steady-state current. Support for this amendment can also be found throughout the specification, for example at paragraph [0056] of the

published application. Claim 10 recites that the at least one counter electrode or counter/reference electrode is a single electrode. Support for this amendment can be found throughout the specification, for example at paragraph [0050] and FIGS. 1-4 of the published application. Finally, claim 11 recites that the circuitry is configured to maintain an approximately fixed potential to determine the diffusion coefficient and concentration of the redox mediator. Support for this amendment can likewise be found throughout the specification, for example at paragraphs [0054] and [0055] of the published application.

No new matter is added.

Summary of the Arguments

Neither of the two reference that the Examiner relies upon to teach “means for measuring from cell current the diffusion coefficient of a redox mediator in the cell and independently its concentration” (which has been replaced by the language “circuitry configured to determine the diffusion coefficient of a redox mediator in the cell, and independently its concentration, from cell current”) are compatible with the disclosures of Diebold and White. The two references, Denuault and Daruházi, both rely on non-Cottrell equations to make their determinations while the teachings of Diebold and White are specifically directed to devices that rely on Cottrell equations. By definition, a device relying on Cottrell equations *cannot* achieve a steady state current, while the devices of Denuault and Daruházi both *rely* on achieving a steady state current to make accurate measurements. Thus, combining the non-Cottrell teachings of Denuault or Daruházi with the Cottrell devices that result from combining Diebold and White is not possible, or will at least cause significant and undesirable errors if made.

With respect to Denuault, the teachings rely on microdisk and microsphere electrodes to calculate a steady state current based on the diffusion geometry created by such electrodes. While the Examiner asserts that the inclusion of the radius in the Denuault calculations is merely a correction factor, it is clear that *but for* the reliance on the radius in the Denuault calculations, a steady state current could not be achieved; elimination of this factor would necessarily result in a Cottrell current. The planar electrodes of Diebold and White do not have a similar diffusion geometry, and thus cannot rely on the edge effects inherent in microdisk and microsphere electrodes as the teachings of Denuault do.

With respect to Daruházi, the disclosure fails to teach what the Examiner alleges it teaches. There is no indication that Daruházi teaches independent determinations of the diffusion coefficient (D) and the concentration of glucose (c^o). Daruházi only teaches determining the diffusion coefficient (D) and the spacing between electrodes (δ). To that end, in order to make that determination, Daruházi teaches finding the value of the diffusion coefficient (D) *in literature*. Looking up the value of the diffusion coefficient (D) is not an *independent determination* of the diffusion coefficient as required in the claims. The reason Daruházi cannot make an independent determination of both variables is because it relies on achieving a steady state current (thus also making it incompatible with Diebold and White because it is non-Cottrell), and only a ratio defining the dependent relationship between the diffusion coefficient (D) and the spacing between the electrodes (δ), or between the diffusion coefficient (D) and the concentration of glucose (c^o), can be determined.

Daruházi is further incompatible with the teachings of Diebold and White because it relies on cyclic voltammetry to make its measurement determinations. Cyclic voltammetry, as taught by Daruházi, requires multiple potential sweeps that use additional external electronics and take at least four and one-half minutes to be performed. No person having ordinary skill in the art would ever combine cyclic voltammetry teachings like those of Daruházi with a fast-acting cell like those that result from the teachings of Diebold and White.

Accordingly, neither Denuault nor Daruházi can be combined with Diebold, White, and the other cited references to arrive at the claimed invention.

Rejections Pursuant to 35 U.S.C. § 103(a)

Claims 1-4 and 6

The Examiner rejects claims 1-4 and 6 pursuant to 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,437,999 of Diebold et al. ("Diebold") in view of U.S. Patent No. 5,089,320 of Straus et al. ("Straus"), U.S. Patent No. 5,095,407 of Kanezawa et al. ("Kanezawa"), a June 2001 Imaging Technologies Update from Enthone ("Enthone"), U.S. Patent No. 5,243,516 of White ("White"), and either of two articles from the Journal of Electroanalytical Chemistry, one of which is entitled "Direct Determination of Diffusion Coefficients by Chronoamperometry at Microdisk Electrodes" by Denuault et al. ("Denuault"), and the other of which is entitled "Cyclic Voltammetry

for Reversible Redox-Electrode Reaction in Thin Layer Cells with Closely Separated Working and Auxiliary Electrodes of the Same Size” by Daruházi et al. (“Daruházi”). In particular the Examiner argues that the combination of Diebold, Straus, Kanazawa, Enthone, and White teaches the claimed invention except for the “means for measuring from cell current the diffusion coefficient of a redox mediator in the cell and independently its concentration.” The Examiner relies on the teachings of Denuault or Daruházi to remedy the deficiencies of the combination of the other references. We respectfully disagree.

Cottrell Current vs. Non-Cottrell Current

In order to understand why teachings like those of Denuault and Daruházi, which teach non-Cottrell current, cannot be used in devices and methods like those of Diebold and White, which teach the use of a Cottrell current in conjunction with the operation of electrochemical sensors, it must first be understood that Cottrell currents and non-Cottrell currents are not compatible.

A Cottrell current is defined by the following equation:

$$i = \frac{nFA\sqrt{DC_0}}{\sqrt{\pi t}}$$

where:

- i is the current measured;
- n is the number of moles of electrons transferred per mole of electroactive species reacted;
- F is Faraday’s Constant;
- A is the electrode area;
- D is the diffusion coefficient of the electroactive species;
- C_0 is the concentration of the electroactive species; and
- t is time.

(See col. 1, line 67 to col. 2, line 14 of White.) An inspection of this equation illustrates that a steady-state current *can never be achieved*. This is because Cottrell currents are caused in response to depletion of an electroactive species around an area of an electrode. Current and time are inversely proportional. Accordingly, as time continues to lapse, the current continues to dissipate. *It is mathematically impossible for a Cottrell current to achieve steady-state.*

Further, an inspection of the Cottrell equation illustrates that the only parameters that can be

known independently are: (1) the current (i) at various intervals of time (t); (2) the number of moles of electrons transferred per mole of mediator reacted (n); (3c) the area of the working electrode (A); and (4) Faraday's constant (F). Assuming each of these factors are known, it is impossible in a Cottrell equation to independently determine the diffusion coefficient (D) and the concentration of the electroactive species (C_o) because they are mathematically dependent on each other. As Applicants recognized from the outset, "[b]y measuring the Cottrell current at known times after application of a potential to the sensor electrodes it is only possible to determine the product concentration times square root of the diffusion coefficient [$C_o\sqrt{D}$] and therefore *it is not possible to determine the concentration of the mediator independent of its diffusion coefficient.*" (Para. [0056] of the published application; emphasis added.)

Non-Cottrell current, on the other hand, is any current that is not governed by the aforementioned equation. While non-Cottrell currents can come in many forms, unlike Cottrell currents, a steady-state current can be achieved. There is no mathematic impossibility that prevents at least some non-Cottrell currents from achieving a steady-state.

The present invention, as well as the devices discussed in Denuault and Daruházi, each are directed to devices that measure the concentration of electroactive species using non-Cottrell currents. Diebold and White, on the other hand, are directed to Cottrell currents. Because Diebold and White are thus incapable of achieving steady-state currents, solutions for solving non-Cottrell current values that do achieve a steady-state cannot be used to solve for the unknown values in the Cottrell equation. Although cliché, it truly is like comparing apples and oranges.

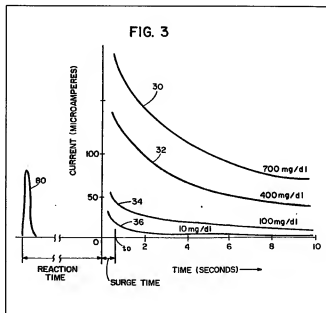
Diebold and White

Diebold discloses an electrochemical sensor that includes a reference or counter electrode element spaced apart from a working electrode element by a spacer. (*See at least* col. 8, lines 17-19.) Each electrode element is a multi-layered structure, and includes an insulating substrate, a metalized layer, and a second insulating substrate. (*See at least* col. 4, line 34 to col. 5, line 15.) The exposed portion of the metalized layer defines Diebold's electrode. (*See at least* col. 8, lines 26-29.) A person having ordinary skill in the art would recognize that this configuration is that of a planar electrode. A planar electrode, as understood by one having ordinary skill in the art, does not refer to the shape of the electrode, but rather, refers to the geometry of diffusion volume surrounding the electrode. In Diebold, the electrode is planar because the electroactive species diffuses to the

electrode from an essentially flat planar volume. (See col. 12, line 68 to col. 13, line 8.) This is different than a microdisk electrode, in which the electroactive species diffuses to the electrode from a hemispherical volume. (See p. 29, para. 3 of Denuault.) In order to form a biosensor, Diebold teaches inserting its electrochemical sensor into a small meter device like the biosensing instrument disclosed in White. White, as discussed in greater detail below, teaches a biosensing instrument that has a Cottrell current. Diebold fails to teach or even suggest the use of its electrochemical sensor in a way that is non-Cottrell.

White discloses a biosensing instrument that uses Cottrell current in order to make measurements with respect to current and time. (See at least col. 2, lines 62-64.) In fact, the whole purpose of the White invention is to attempt to correct errors that occurred in previous biosensing instruments that used the Cottrell equation by recognizing that the current in those systems had non-Cottrell behavior and thus classifying the results of the prior art systems referred to in White as *invalid*. (See at least *id.* at lines 35-59, col. 7, lines 38-47, and claims 1-8, i.e., every claim of White; emphasis added.) FIG. 3 of White, which was discussed during the interview and is reproduced to the right, illustrates current variations that occur with various levels of glucose concentration. (Col. 4, lines 16-18.) The curves (30, 32, 34, and 36) illustrate the changes of current with the passage of time, after a potential is applied between electrodes. (*Id.* at lines 20-23.) As

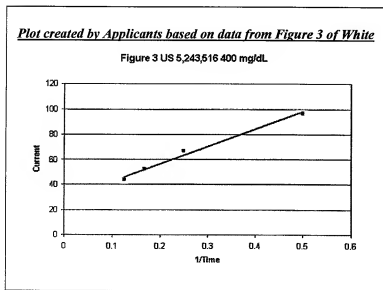
explicitly stated by White, the shape of each of the current curves (30, 32, 34, and 36) is described by equation 1 of White, i.e., the Cottrell equation. (*Id.* at lines 27-28 and col. 2, lines 5-14.) Thus, a person having ordinary skill in the art would recognize that determinations of how the current changes with time based on equation 1 are fully accurate, while determinations based on an interpretation of a descriptive figure like Figure 3, as the Examiner proposed during the interview, are certainly not as reliable. The fact remains that, in a system described by the Cottrell current, in which the value of each of the variables except for time is known, the current can never achieve a steady-state because as t continues to increase, the value of the current continues to decrease; the



decrease of current is inversely proportional to the square root of time. Because the curves (30, 32, 34, and 36) of White represent the value of the Cottrell current with respect to time, it is *mathematically impossible* for the curves (30, 32, 34, 36) to ever arrive at a steady-state current.

Further, although Figure 3 is merely descriptive and thus is not nearly as reliable for determining a measurement of current versus time than the actual equation that Figure 3 is based from, extracting data from Figure 3 actually *confirms* Cottrell behavior because the results illustrate that a steady state *is not achieved*. If a person having ordinary skill in the art attempted to extract data from Figure 3, he or she would attempt to measure points from the graph that indicate the largest variations over the range where the y-axis is definitively marked (it is of note that there is no indication as to what value the top-most mark on the y-axis represents, which further supports the fact that relying on the results from equation 1 is superior to relying on determinations made from reviewing a descriptive figure). Using the 400 mg/dl curve, a plot of the current against the reciprocal of time yields the plot provided herein. This plot confirms Cottrell behavior with no

evidence of steady state current because the current continues to change as time elapses. Thus, while to an untrained eye the descriptive figure of White could be viewed as achieving a steady state, the actual facts based on the equation used to create Figure 3 of White, and the results of the current with respect to time plotted based on the data provided by Figure 3, prove that no steady state current can be achieved in White.



Accordingly, both Diebold and White teach devices and methods that operate using a Cottrell current. By definition, as illustrated by the mathematical formula, if a current is a Cottrell current, a steady-state cannot be achieved and the diffusion coefficient and concentration cannot be determined independently.

Denuault and Daruházi

The Examiner maintains that the teachings or either Denuault or Daruházi will allow a person having ordinary skill in the art to more accurately determine the Cottrell current using the algorithm of White in the electrochemical sensor of Diebold. The Examiner states that both Denuault and Daruházi disclose means for measuring from cell current the diffusion coefficient of a redox mediator in a cell and independently its concentration. More particularly, the Examiner argues that the means of both Denuault and Daruházi allow the value of the diffusion coefficient to be actually determined, and that determining such value allows for the more accurate determination of the Cottrell current of the cell of Diebold using the algorithm of White. This argument, however, fails to account for the fact that both Denuault and Daruházi are directed to systems that use non-Cottrell current. Cottrell currents and non-Cottrell currents *are not compatible*. This is because of the physical, electrochemical requirements of the two systems. In a Cottrell system, the electrochemical species near the electrode is depleted, while in non-Cottrell systems the electroactive species near the electrode is not depleted. A Cottrell system generates a current versus time plot that subsequently follows the Cottrell equation, while a non-Cottrell system generates a current versus time plot that is non-Cottrell in nature. A person having ordinary skill in the art would recognize that one variable cannot be solved for based on a current versus time trace that is non-Cottrell and then plugged into another equation that is Cottrell to solve for another variable. The result would be invalid. A current versus time trace is either non-Cottrell or Cottrell; it cannot be both. This approach, however, is exactly the approach the Examiner proposes.

Denuault

As discussed with the Examiner during the interview, the teachings of Denuault are directed to microdisk and microsphere electrodes. Both microdisk and microsphere electrodes are not *planar* electrodes. A planar electrode does not refer to the shape of the electrode, but rather the geometry of diffusion volume surrounding the electrode. The diffusion volume surrounding a planar electrode is a flat planar volume; the diffusion volume surrounding both a microdisk electrode and a microsphere electrode is a hemispherical volume. (*See at least* p. 29, para. 3 of Denuault.) In fact, Denuault recognizes that planar electrodes and microdisk electrodes are two different types of electrodes at page 28, paragraph 2, listing a planar electrode, a rotating disk electrode (RDE), and a microdisk electrode as types of electrodes that have different sizes and geometries. A person having ordinary

skill in the art would recognize that an electrode cannot be both a planar electrode and a microdisk electrode because the electrode cannot have two different diffusion volumes surrounding the electrode.

Not only are the geometries of the diffusion volume surrounding the electrodes different for planar electrodes and microdisk electrodes, but the analyses used to calculate variables such as the diffusion coefficient for the two types of electrodes are different. As discussed with the Examiner during the interview, and as previously discussed with the Examiner in light of an article from the Bulletin of the Korean Chemical Society entitled "Simultaneous determination of Diffusion Coefficient and Concentration by Chronoamperometry at a Microdisk Electrode" by Jung et al. ("Jung"), microdisk electrodes have edge effects which allow for a diffusion coefficient to be calculated. Similar edge effects are not produced by planar electrodes, which is why Jung specifically teaches that its analysis methods are not compatible with planar electrodes. (See beginning of first full paragraph of first column of page 210 to fourth full paragraph of first column of page 211 of Jung, which is attached for the Examiner's convenience.) It is worth noting that Jung also supports the fact that microdisk electrodes *cannot* be planar electrodes.

Similar to Jung, the analysis methods of Denuault are also incompatible with planar electrodes. The calculations taught by Denuault, in fact, *require* a value for a disk radius. (See Abstract on page 27, stating that the method "requires only a value for the disk radius"; and the first paragraph of the INTRODUCTION on pages 27-28, stating that the method "requires only knowledge of the disk radius (*a*).") Specifically, Denuault teaches that a steady-state current can be calculated using the following equation:

$$i_s(t) = \frac{nFAD^{1/2}c^*}{\pi^{1/2}t^{1/2}} + \frac{nFADc^*}{r_s}$$

where:

- $i_s(t)$ is the steady-state current measured;
- n is the number of moles of electrons transferred per mole of electroactive species reacted;
- F is Faraday's Constant;
- A is the electrode area;
- D is the diffusion coefficient of the electroactive species;
- c^* is the concentration of the electroactive species;
- t is time; and

- r_s is the radius of the microdisk electrode.

The Examiner asserts that the second factor, $\frac{nFADc^*}{r_s}$, is just a correction factor for the round shape of the microdisk electrode and thus can just be eliminated. Doing so, however, would result in the Cottrell equation: $i(t) = \frac{nFAD^{1/2}c^*}{\pi^{1/2}t^{1/2}}$. As discussed above with respect to White, just the Cottrell equation alone *cannot* yield a steady-state current. *It is mathematically impossible.*

The second factor, contrary to the Examiner's assertion, is not just a correction factor, but rather, is a reflection of the fact that the diffusion geometry is hemispherical rather than planar. It is not at all a consequence of whether or not the electrode is round or square. What determines whether or not the diffusion geometry is planar or hemispherical is the relative contribution of material diffusing from liquid surrounding the edges of the electrode to material diffusing from liquid surrounding the rest of the electrode away from the edges. If the area of the electrode is large compared to the area close to its edges, or, alternatively, the electrode edges are masked so they are not surrounded by liquid at all, then there will be essentially planar diffusion. If the area of the electrode is small compared to its edges, such as in a microdisk or microsphere electrode, then it will have essentially hemispherical diffusion.

It is only because of this second factor in the Denuault equation that a steady-state current can be calculated. The second factor includes the radius of the microdisk electrode, thereby illustrating that accounting for the radius of the electrode is required in order to calculate the steady-state current. As reflected by the Cottrell equation, the radius of a planar electrode (if it happened to be round) only contributes in so much as it helps to define the electrode area A . The radius has no further effect on the current measured, and thus cannot be used in the methods of Denuault, which require the electrode area A and radius r_s to be used separately.

Planar electrodes like those of Diebold do not have a radius, and thus cannot be used in the methods of Denuault. In fact, each of the current calculations discussed by Denuault includes a radius. (See THEORY section on page 29, illustrating calculations used to determine the diffusion coefficient D , which is a function of the radius a of the microdisk; equations 10-13; the last paragraph on page 31; and page 32, including equation 14.) Not surprisingly, Denuault fails to provide a single teaching that does not rely on the value of the radius of a microdisk or microsphere

electrode. That is because it is only these types of electrodes that allow a steady-state current to be achieved in order to measure a diffusion coefficient. These non-Cottrell behaviors are incompatible with the teachings of Diebold and White. The Denuault equation requires a steady-state be achieved, but no steady-state current can be achieved with a Cottrell current response like those of Diebold or White.

Accordingly, the teachings of Denuault cannot be applied to either Diebold or White as the Examiner proposes; it would lead to an inoperable device fraught with errors.

Daruházi

Similar to Denuault, Daruházi also teaches achieving a steady-state current and thus is not compatible with the teachings of Diebold and White. Further, Daruházi does not even teach a method for independently determining both a diffusion coefficient and a concentration of a redox mediator. To the extent that Daruházi does include teachings that would allow these two variables to be independently determined, a person having ordinary skill in the art would not have applied the teachings of Daruházi to the teachings of either Diebold or White at the time of Applicants' invention.

Incorporating the teachings of Daruházi with the devices of Diebold and White would render the devices of Diebold and White unsatisfactory for their intended purposes

Daruházi relies on achieving a steady-state current in order to perform its desired calculations. (*See at least* page 78, para. 2, explaining that the determinations made by its cell are the result of an enhanced current response and a steady-state current; p. 79, the paragraph under equation 3, stating that it is assumed that t_r is long enough *to reach the steady-state*; emphasis added; p. 81, equation 32, illustrating that the value of the steady-state current, I_{ss} , is based, in part, on the values of the diffusion coefficient, D , the concentration of glucose, c^o , and the distance between the electrodes, δ ; and p. 87, paras. 4-5, indicating that the determination of a ratio comparing the diffusion coefficient, D , and the distance between the electrodes, δ , is based on achieving stable steady-state current values.) In particular, the portion of Daruházi that the Examiner relies upon to argue that the diffusion coefficient (D) and the concentration of glucose (c^o) can be independently determined, i.e., paragraph 4 on page 87, specifically states that slow potential sweeps are performed and a ratio δ/D is determined from equation 32. (Emphasis added.) Equation 32, found on page 81

of Daruházi, indicates that a steady-state current value is based, in part, on the values of the diffusion coefficient (D), the concentration of glucose (c^o), and the distance between the electrodes (δ):

$$I_{ss} = \frac{nFADc^o}{\delta}$$

where:

- I_{ss} is the steady-state current measured;
- n is the number of moles of electrons transferred per mole of electroactive species reacted;
- F is Faraday's Constant;
- A is the electrode area;
- D is the diffusion coefficient of the electroactive species;
- c^o is the concentration of the electroactive species; and
- δ is the distance between the working electrode and the auxiliary electrode.

This equation is *not* dependent on time because it relies on *achieving a steady-state*. As discussed above with respect to Denuault, a steady-state current, which cannot be a Cottrell current by definition, is not compatible with devices and methods that rely on Cottrell current (e.g., the devices and methods disclosed in Diebold and White). At least because Daruházi, like Denuault, relies on methods requiring the achievement of a steady-state current, the methods of Daruházi cannot be combined with Diebold and White. The resulting device would be inoperative, and thus unsatisfactory for its intended purpose.

Combining the teachings of Daruházi with the devices of Diebold and White is not sufficient to establish *prima facie* obviousness

To the extent that the Examiner still wrongly believes that the teachings of Daruházi can be combined with the teachings of Diebold and White to arrive at the present invention, the claims are still not obvious because Daruházi fails to teach or even suggest a method for *independently* determining both a diffusion coefficient of a redox mediator *and a concentration of the redox mediator*. As explained in the previous Office Action response, Daruházi only directs its teachings to determining a diffusion coefficient of a substrate and *a distance between working and auxiliary electrodes* simultaneously. (See ABSTRACT; emphasis added.) Throughout Daruházi, it is assumed that the value of the concentration of glucose is a known value. No determination is *ever* made for the *concentration of glucose* using the methods taught by Daruházi. Accordingly, Daruházi fails to teach or even suggest a method for determining both a diffusion coefficient of a redox mediator *and*

a concentration of the redox mediator as required in the claimed invention.

The Examiner appears to argue that in a system where the distance between electrodes (δ) is known, that the same method discussed on the fourth paragraph of page 87 can be used to determine both a diffusion coefficient of a redox mediator *and a concentration of the redox mediator*. This argument, however, fails to account for the fact that the methods of Daruházi fail to teach or suggest a way to *independently determine* the two unknown variables of equation 32.

Daruházi only teaches determining a ratio comparing the distance between the electrodes (δ) to the diffusion coefficient (D). (See p. 87, para. 4.) A person having ordinary skill in the art would recognize that it is impossible to solve for both D and δ using the single equation: $I_{ss} = \frac{nFADc^0}{\delta}$.

This is why Daruházi teaches determining *the ratio* of δ/D . In Daruházi, the value being solved for is the distance between the electrodes (δ). In order to solve this distance, Daruházi relies on the literature value of the diffusion coefficient (D). (See p. 87, para. 5.) *There is no independent determination of the value of the diffusion coefficient (D) based on the particular set-up of Daruházi.* This is completely contrary to the present invention in which *an independent determination* of both of the unknown values is made; neither value *is looked up in the literature*.

Similarly, if the distance between the electrodes (δ) were known and the concentration of glucose (c^0) was unknown, these same problems would still exist. Only a comparative relationship could be made between the diffusion coefficient (D) and the concentration of the glucose (c^0). Determining the value of the concentration of the glucose (c^0) could only occur if the value of the diffusion coefficient (D) from literature was used. This is exactly the type of generic, error-ridden determination that the present invention is designed to avoid. The present invention *independently* determines both the value of the diffusion coefficient (D) and the concentration of the redox mediator (c^0). Daruházi, on the other hand, teaches solving for a dependent, comparative relationship between two unknown values and solving for one of those values by relying on a value from literature.

The Examiner's proposed combination does not even teach the claimed invention, and thus a *prima facie* case of obviousness cannot be established.

A person having ordinary skill in the art would not combine the slow potential sweep teachings of Daruházi with electrochemical sensors like those of Diebold or White

Still further, although it should be clear by now that Daruházi fails to teach the aspect of the present invention that the Examiner relies upon Daruházi to teach, even if Daruházi somehow did teach a method for independently determining both the diffusion coefficient and the concentration of a redox mediator, a person having ordinary skill in the art would not make the Examiner's proposed combination. This is at least because, as discussed above, such teachings would be incompatible. Daruházi relies on a non-Cottrell current (e.g., steady-state) while Diebold and White rely on a Cottrell current (which is non-steady-state by definition). The incompatibility between the teachings of Daruházi and the teachings of Diebold and White are a function of electrochemistry. A person having ordinary skill in the art also would not make the Examiner's proposed combination because such a person would never incorporate the slow potential sweep process disclosed by Daruházi into the teachings of either Diebold or White.

As explained in *KSR International Co. v. Teleflex, Inc.*, "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there *must be some articulated reasoning with some rational underpinning* to support the legal conclusion of obviousness." (MPEP § 2142, citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); emphasis added; *see also* MPEP § 2143.01.) It is not enough to pick and choose features from various pieces of art and just combine them to arrive at the claimed invention without any support for making such combinations. (*In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596 (Fed. Cir. 1988).) The Examiner must guard against impermissible hindsight that results from the knowledge of the invention of the present application and the Examiner may not "use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." (*In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (citation omitted).)

The proposed combination relies on impermissible hindsight

The present rejection is an exemplary illustration of a situation in which the Examiner is relying on the present invention as an instruction manual or "template" to piece together various disclosures from the prior art to arrive at the claimed invention. The Examiner cites six different references (Diebold, in view of Straus, Kanazawa, Enthone, White, and one of Denuault or Daruházi)

to arrive at the present invention. The Examiner starts with Diebold, and then based on the teachings of the present invention, pieces disclosures from each of the other references to arrive at the present invention. With particular reference to the teachings of Daruházi, no person having ordinary skill in the art, in view of Daruházi, Diebold, and White, would have an articulated reason or rational underpinning for making the Examiner's proposed combination. This is likely because, as discussed above, the teachings of Daruházi are incompatible with the devices and methods of Diebold and White. Of course, even if the slow potential sweep method of Daruházi was some how compatible with the devices and methods of Diebold and White, no person having ordinary skill in the art would have made the combination at the time of Applicants' invention.

The long time it takes to perform the sweep methods of Daruházi would prohibit a combination of the Daruházi teachings with the devices of Diebold and White

Daruházi relies on cyclic voltammetry to make its measurement determinations. (*See at least* ABSTRACT on p. 77.) In particular, a slow potential sweep is performed in order to determine the ratio of δ/D . (*See* p. 87, para. 4.) A person having ordinary skill in the art would recognize the unfavorable amount of time such a slow sweep takes to perform. The amount of time it would take to perform such a sweep would likely be much greater than the time it would take to perform the methods of White in conjunction with the cell of Diebold. Even assuming that the teachings of Daruházi would lead to more accurate results (which is not true given the errors that would occur trying to apply non-Cottrell teachings to a Cottrell current cell), a person having ordinary skill in the art would not look to teachings related to potential sweeps. The length of time it takes to perform such a sweep would be prohibitive. A glucose meter like that of Diebold is designed to act quickly to provide a fast determination of the concentration of glucose in a sample of blood.

While Applicants believe that a person having ordinary skill in the art would readily recognize the undesirable length of time it would take to perform a sweep if incorporated with a cell like Diebold, a thorough reading of Daruházi makes it clear that the amount of time it would take would not be desirable. Daruházi requires a series of experiments in order to make its determination, while Diebold and White only require a single experiment. (*See* para. 3 of p. 87 of Daruházi.) Diebold indicates that the time to conduct an experiment is about 10 seconds, while White indicates that the time to conduct an experiment is between 10 and 30 seconds. (*See at least* col. 13, lines 4-6 and Figure 9 of Diebold and col. 5, lines 44-48, col. 6, lines 19-20, and Figure 3 of White.)

Daruházi, on the other hand, requires approximately at least 260 seconds. This time can be derived based on the information provided on page 87 and in Figure 6. Figure 6 shows the potential of the working electrode is swept between -0.2 V and $+0.9\text{ V}$. Paragraph 1 on page 87 discloses a “slow potential sweep rate” of 5 mV/s and paragraph 2 on the same page discloses a “fast potential sweep” rate of 50 mV/s . Paragraph 3 on page 87 of Daruházi explains that a “series of experiments” are required in order to determine the variables. Relying on all of these disclosures, it can be determined that a series of experiments as taught by Daruházi would result in the following process:

- Performing a slow potential sweep between -0.2 V and $+0.9\text{ V}$ at 5 mV/s ; this would take approximately 240 seconds;
- Performing a reverse sweep in order to bring the system back to a desired starting configuration, or allowing the system to relax with the voltage disconnected (for purposes of this calculation, no additional time is added, although certainly this step would require some amount of time to elapse); and
- Performing a second potential sweep between -0.2 V and $+0.9\text{ V}$, but at 50 mV/s ; this would take approximately 24 seconds;

Thus, just based on the two sweeps provided for in Daruházi, *without* accounting for the time required to reset the system in between the two sweeps, approximately at least 264 seconds (i.e., nearly four and one-half minutes) elapse when performing the methods disclosed by Daruházi. This length of time is incompatible with glucose sensor tests in devices like those disclosed by Diebold and White. Still further, even if these teachings were used in conjunction with Diebold and White, it is likely that a whole blood sample as disclosed by Diebold and White would clot during this extended period of time in which the test is performed. This is yet another reason why this combination is inoperable. Accordingly, in trying to improve the accuracy of such a meter, a person having ordinary skill in the art would not have considered methods that substantially increase the length of time to make a determination of the concentration of glucose in a sample of blood.

The difficulty of incorporating the electronics of Daruházi would prohibit a combination of the Daruházi teachings with the devices of Diebold and White

Similarly, a person having ordinary skill in the art would also know that the electronics required to perform a potential sweep like the sweep of Daruházi are much different than the types of electronics taught by Diebold and White. Incorporating electronics related to performing a potential sweep into the devices and methods of Diebold and White would be both difficult and undesirable.

External electronic circuitry is required to sweep the voltage of the working electrode up and/or down. The response of the current is measured as a function of the voltage of the working electrode. Thus, in order to employ this technique, the potential or voltage of the working electrode must be known and must be able to be controlled externally. A person having ordinary skill in the art would recognize that this requires three electrodes. (*See at least* para. 1 of Theory section on p. 78 and para. 1 of Experimental section on p. 83.)

Further, external electronics are connected such that there is a very high impedance in the circuit between the working and reference electrode and a relatively low impedance between the working and the counter or auxiliary electrode. The electronics apply a voltage between the working and auxiliary or counter electrodes that causes a current to flow therebetween, and the voltage applied is adjusted (i.e., swept) by the electronics so that the voltage difference between the working and reference electrodes is kept at a desired level. Based on the known potential of the reference electrode and the potential difference between the reference and working electrodes, the potential of the working electrode can be inferred and circuitry used to control it at the desired level. This knowledge and control of working electrode potential is essential in Daruházi because the relationship of the current to the potential of the working electrode is what is required in the cyclic voltammetry method.

The two electrode systems of Diebold and White fail to include the separate reference electrode and also fail to include the electronics associated therewith. This is because the methods taught by these two references do not need these additional components in order to perform their calculations. Of course, none of the teachings of Diebold and White would allow for the calculations of Daruházi to be performed as the cells are constructed because the cells of Diebold and White only include two electrodes. It is not possible to know the potential of the working electrodes of Diebold and White because the respective counter electrode does not have a known reference potential. Further, if only a reference electrode and working electrode are used, then either the mediator in the solution (e.g., ferricyanide) will interfere with the potential of the reference electrode in an unknown way, thereby again not allowing for a measurement of the potential of the working electrode, or the mediator would not react appreciably at the reference electrode, in which case the electrochemical conditions required for the teachings of Daruházi to work would not be present. It is a condition for the teachings of Daruházi to work that the redox species be regenerated at the auxiliary electrode to establish a steady state current. (*See at least* Abstract on p. 77.) If the mediator does not react

appreciably at a reference electrode, as would be the case if combined with the teachings of Diebold and White, the redox species would not be regenerated and thus the teachings of Daruházi would fail. It is thus clear that the two electrode systems of Diebold and White could not function in the way required for the teachings of Daruházi to be successful with the configurations of Diebold and White.

Accordingly, the teachings of Daruházi cannot be applied to either Diebold or White as the Examiner proposes. The teachings are incompatible, and thus create a device that is unsatisfactory for its intended purpose in combination. Further, Daruházi does not even teach a method of independently determining both a diffusion coefficient and a concentration of a redox mediator, and thus a *prima facie* case of obviousness is not made. Finally, the proposed combination would not have been made at the time of Applicants' invention by a person having ordinary skill in the art because it is made with the benefit of impermissible hindsight, would create a device that takes much longer to operate than presently designed, and would require a difficult and undesirable incorporation of electronics to the device.

For all of the aforementioned reasons, independent claim 1, as well as claims 2-4 and 6 which depend therefrom, distinguishes over Diebold in view of Straus, Kanezawa, Enthone, White, and Denuault or Daruházi and thus represents allowable subject matter.

Claim 5

The Examiner rejects claim 5 pursuant to 35 U.S.C. § 103(a) as being obvious over Diebold in view of Straus, Kanezawa, Enthone, White, and Denuault or Daruházi, further in view of U.S. Patent No. 5,126,034 of Carter et al. ("Carter") and U.S. Patent No. 5,399,256 of Bohs et al. ("Bohs").

As noted above, Diebold in view of Straus, Kanezawa, Enthone, White, and Denuault or Daruházi do not teach or even suggest an electrochemical biosensor that includes both a hollow electrochemical cell and circuitry configured to determine the diffusion coefficient of a redox mediator in the cell, and independently its concentration, from cell current as claimed by Applicants. Carter and Bohs fail to remedy the deficiencies of Diebold, Straus, Kanezawa, Enthone, White, and Denuault or Daruházi. Accordingly, at least because it is dependent upon an allowable base claim (independent claim 1), claim 5 distinguishes over Diebold in view of Straus, Kanezawa, Enthone, White, and Denuault or Daruházi, further in view of Carter and Bohs, and thus represents allowable

subject matter.

Claims 7-11

Each of new dependent claims 7-11 are allowable, both because they depend from allowable base claim 1, and further because each includes independently allowable subject matter.

Claim 7 recites that the circuitry includes a microprocessor. None of Diebold, Straus, Kanezawa, Enthone, White, Carter, Bohs, Denuault, and Daruházi teach a microprocessor as part of circuitry configured to determine the diffusion coefficient of a redox mediator in the cell, and independently its concentration, from cell current. Specifically with respect to Denuault and Daruházi, the methods disclosed therein do not teach circuitry or a microprocessor. Accordingly, claim 7 is allowable both because it depends from an allowable base claim, but also because it recites independently allowable subject matter.

Claim 8 recites that the working and counter or counter/reference electrodes of the electrochemical biosensor are planar electrodes. While the electrodes of Diebold are also planar electrodes, Diebold fails to disclose a way to determine the diffusion coefficient of a redox mediator in the cell, and independently its concentration, from cell current. This is because Diebold uses a Cottrell current, which *cannot* make such an independent determination. As discussed above, Denuault teaches the use of microdisk and microsphere electrodes, however, microdisk and microsphere electrodes are not planar electrodes. The teachings of Denuault will not work with planar electrodes, and thus just as Denuault cannot be combined with Diebold and White to teach the invention of claim 1, it also cannot be combined with Diebold and White to teach a cell having planar electrodes that can determine the diffusion coefficient of a redox mediator in the cell, and independently its concentration, from cell current. Daruházi also cannot be combined with the teachings of Diebold and White to arrive at the invention of claim 1, and thus also cannot be combined with the teachings of Diebold and White to arrive at the invention of claim 8. Accordingly, claim 8 is allowable both because it depends from an allowable base claim, but also because it recites independently allowable subject matter.

Claim 9 recites an electrochemical biosensor that has circuitry configured to achieve a steady-state current. As discussed above, it is *impossible* for the Cottrell current devices and methods of Diebold and White to achieve a steady-state current. Although teachings like Denuault

and Daruházi do teach the use of a steady-state current, these teachings cannot be incorporated into the teachings of Diebold and White because they are incompatible. Accordingly, claim 9 is allowable both because it depends from an allowable base claim, but also because it recites independently allowable subject matter.

Claim 10 recites an electrochemical biosensor that includes only one counter or counter/reference electrode. In order to incorporate the teachings related to a slow potential sweep of Daruházi into Diebold, at least two counter or counter/reference electrodes are needed. This is because a second counter or counter/reference electrode is needed to determine the potential of the working electrode during the sweep. (*See at least* p. 83, last paragraph of Daruházi, which teaches the use of two glassy carbon electrodes and a saturated calomel electrode to serve as the reference electrode.) A person having ordinary skill in the art would recognize that the potential sweep method taught in Daruházi is inoperable with only one counter or counter/reference electrode. Thus, even if the teachings of Daruházi could somehow be incorporated into the devices and methods of Diebold and White, the resulting device would include at least two counter or counter/reference electrodes. Accordingly, claim 10 is allowable both because it depends from an allowable base claim, but also because it recites independently allowable subject matter.

Claim 11 recites an electrochemical biosensor that has circuitry configured to maintain an approximately fixed potential to determine the diffusion coefficient and concentration of the redox mediator. If the teachings of Daruházi were incorporated into the devices and methods of Diebold and White, an approximately fixed potential could not be maintained to determine the diffusion coefficient and concentration of the redox mediator. A potential sweep, like the one taught in Daruházi, requires a variety of potentials be used, and thus an approximately fixed potential cannot be maintained. (*See at least* p. 79, para. 1 and equations 2 and 3.) Thus, even if the teachings of Daruházi could somehow be incorporated into the devices and methods of Diebold and White, the resulting device would not include circuitry configured to maintain an approximately fixed potential to determine the diffusion coefficient and concentration of the redox mediator. Accordingly, claim 11 is allowable both because it depends from an allowable base claim, but also because it recites independently allowable subject matter.

Conclusion

In view of the reasons set forth above, each of the presently pending claims in this application is believed to be in condition for allowance, and reconsideration is respectfully requested. The Examiner is urged to telephone the undersigned Attorney for Applicants in the event that such communication is deemed to expedite prosecution of this matter.

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Respectfully submitted,



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